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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/633,407 | 08/01/2003 | Douglas W. Losordo | 58098 (71417) | 6007 |

21874 7590 11/25/2009

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| EXAMINER | |
|---|---|
| HISSONG, BRUCE D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 11/25/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/633,407 | LOSORDO ET AL. | |
| | Examiner | Art Unit | |
| | Bruce D. Hissong, Ph.D. | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,17,24-27,30,38,39,67,68 and 81-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,17,24-27,30,38,39,67,68 and 81-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/26/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

***Formal Matters***

1. Applicants' response to the office action mailed on 5/26/2009, including arguments/remarks and amended claims, was received on8/26/2009 and has been entered into the record.

2. In the response received on 8/26/2009, the Applicants cancelled claims 2-23, 28-37, 40-66, and 69-80, while adding new claims 84-85. Therefore, claims 1, 17, 24-27, 30, 38-39, 67-68, and 81-85 are pending and the subject of this office action.

***Information Disclosure Statement***

The information disclosure statement received on 8/26/2009 has been fully considered.

***Claim Objections***

1. Objection to claim 1 regarding the recitation of an "ezrin modulating agent", as set forth on page 2 of the office action mailed on 5/26/2009, is withdrawn in view of Applicants' arguments that the recitation of "wherein the method comprises decreasing ezrin activity" corresponds to methods of decreasing ezrin activity.

2. Objection to claims 24-27, 38-39, 67-68, and 81-83 for depending from rejected base claims, as set forth on page 2 of the office action mailed on 5/26/2009, is *withdrawn* in view of the rejection of these claims under the new grounds of rejections presented below.

***Rejections Withdrawn***

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejection of claims 1, 17, and 30 under 35 USC § 102(b) as being anticipated by Shibata *et al* , as set forth on pages 4-6 of the office action mailed on 8/26/2009, is *withdrawn* in response to Applicants' arguments that the claims have been amended to recite the limitations of cancelled claim 66, namely that the method comprise isolating endothelial progenitor cells (EPCs) from the mammal and contacting said EPCs with an ezrin modulating agent.

These arguments have been fully considered and are persuasive because Shibata does not teach isolation of EPCs and subsequent contact with an ezrin modulating agent.

## *New Grounds of Rejection/Rejections Necessitated by Amendment*

### *Claim Rejections - 35 USC § 112, first paragraph – written description*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 17, 26-27, 30, 67-68, and 84-85 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of administering an ezrin-modulating agent, wherein said method comprises decreasing ezrin activity, and wherein said methods specifically comprise administration of at least one of an ezrin-modulating agent, cytokine, angiogenic factor, hematopoetic factor, or effective fragments thereof. The claims do not require the administered agents (ezrin-modulating agents, cytokines, angiogenic factor, hematopoetic factors, fragments thereof) of the instant invention to have any biological activity other than to modulate/decrease ezrin activity, nor any particular structure. The specification describes several agents which would function as ezrin modulating agents,

such as TNF-α inhibitors and Rho kinase inhibitors. However, the claims recite administration of not only ezrin modulating agent, but also any cytokine, angiogenic factor, hematopoeitic factor, or an effective fragment of any of these factors. The specification does not describe which of the many possible cytokines, angiogenic factors, hematopoetic factors, or fragments thereof are also capable of modulating ezrin in such a way that ezrin activity is decreased in a mammal. Thus, the genus of cytokines, angiogenic factors, hematopoetic factors, or fragments thereof that are capable of inhibiting/decreasing ezrin activity has not been adequately described in such a way as to convey that the Applicants, at the time of invention, were in full possession of the claimed genus.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a requirement of administering any cytokine, angiogenic factor, hematopoetic factor, or fragment thereof. There is no identification of any particular portion of these factors that must be conserved in order to maintain function, or which of these factors are even capable of mediating the desired function (i.e. inhibition of ezrin activity). Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 24-25 and 38-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Shibata *et al* ("Shibata" – *Circulation*, 2001 (Jan 16), Vol. 103, p. 384-289 – originally cited in the office action mailed on 8/1/2006).

Claims 24-25 of the present invention are drawn to a method of inducing formation of new blood vessels in a mammal, wherein said method comprises decreasing ezrin activity in an amount sufficient to induce formation of new blood vessels by administering to the mammal an ezrin modulating agent that decreases ezrin activity before, during or after the mammal is exposed to conditions conducive to damaging blood vessels. Similarly, claims 38-39 recite a method of reducing the severity of blood vessel damage, wherein said method comprises decreasing ezrin activity in endothelial cells before, during or after the mammal is exposed to conditions conducive to damaging blood vessels.

As discussed in the previous office actions, Shibata teaches administration of Y27632, which the specification discloses to be an ezrin-modulating agent capable of decreasing ezrin activity, to rats which have suffered a balloon injury. Shibata meets the limitations of claims 24-25 because it teaches administration of Y27632 to a mammal that has undergone damage to a blood vessel via the balloon injury. Thus, while Shibata does not specifically teach formation of new blood vessels, it is noted that the patient population in Shibata is the same as currently claimed (i.e. a mammal having a vascular injury), and the method steps of administering the ezrin-modulating agent Y27632 is the same as the claimed method. Therefore, in the absence of evidence to the contrary, it would be expected that the administered Y27632 would induce, to some extent or degree, formation of new blood vessels in the rats of Shibata. Furthermore, regarding the limitations of claim 25, although Shibata does not explicitly teach administration to a rat with ischemic vascular disease, the claims read on administration *before or during* blood vessel damage, and thus Shibata could be considered as administering a rat Y27632 before it developed ischemic vascular disease.

Shibata also meets the limitations of claims 38-39 because the claims read on mammals suffering from balloon angioplasty, and the rats of Shibata have suffered a vascular balloon injury and received the ezrin-modulating agent Y27632. Thus, in absence of evidence to the contrary, the administered Y27632 would be expected to reduce the severity of blood vessel damage to some extent or degree because the patient population and methods of Shibata are the same as those currently claimed. Regarding claim 39, the balloon injured mice could be considered as undergoing blood vessel trauma, meeting the limitations of claim 39. Alternatively, claim 39 recites administration of an ezrin modulating agent *before or during* blood vessel damage, and Shibata could be considered as administering a rat Y27632 before it developed ischemia due to one of the cited conditions.

2. Claims 24-26, 38-39, and 84 are rejected under 35 U.S.C. 102(a) as being anticipated by Krasinski *et al* ("Krasinski" – *Circulation*, 2001 (Oct. 9), Vol. 104, p. 1754-1756 – originally cited in the IDS received on 9/29/2003).

The subject matter of the presently claimed invention has been discussed previously. Krasinski teaches administration of anti-TNF-α antibodies to rats after balloon angioplasty. The specification, on page 15, lines 14-22, teaches that anti-TNF-α antibodies are preferred ezrin-modulating agents capable of decreasing ezrin activity. Therefore, Krasinski teaches administration of an ezrin-modulating agent to mammals suffering from damage to blood vessels, and in the absence of evidence to the contrary, would be expected to induce formation of new blood vessels or reduce the severity of blood vessel damage or modulate endothelial cell proliferation in a mammal because the patient population (mammals undergoing blood vessel damage) and the method steps (administering an agent capable of decreasing ezrin activity) are the same as currently claimed. Furthermore, because the anti-TNF-α antibodies of Krasinski would be expected to induce formation of blood vessels in a mammal to some extent, the antibodies could be considered to be an "angiogenic protein" as recited in claims 26 and 84. Regarding the limitations of claims 25 and 39, as stated above, the claims recite administration of an ezrin modulating agent *before or during* damage to blood vessels, and Krasinski could be considered as administering a rat anti-TNF-α antibodies before it developed ischemic vascular disease or ischemia due to the conditions recited in claim 39.

3. Claims 1, 17, 24-27, 30, 38-39, 67-68, and 81-85 are rejected under 35 U.S.C. 102(e) as being anticipated by Alitalo *et al* ("Alitalo" – US 6,958,147).

The claims of the present invention are drawn to methods for modulating endothelial cell (EC) proliferation, inducing formation of new blood vessels, or reducing the severity of blood vessel damage in a mammal, wherein said method comprises administering an ezrin-modulating agent before, during, or after the mammal is exposed to blood vessel damage. The claims alternately recite the claimed method wherein endothelial progenitor cells (EPCs) are isolated and exposed *ex vivo* to at least one of an ezrin-modulating agent, cytokine, angiogenic factor, or hematopoetic factor, or an effective fragment thereof.

Alitalo teaches administration of VEGF for the treatment or prevention stenosis or restinosis (see abstract). Specifically, Alitalo teaches prevention of restinosis in response to blood vessel damage such as balloon angioplasty (column 1, lines 20-25), and specifically teaches methods of administering VEGF-encoding polynucleotides or VEGF polypeptides to subjects suffering from coronary artery disease and at risk of restinosis (column 3, line 29 – column 5, line 11). Alitalo also teaches ex vivo administration of

VEGF-encoding polynucleotides to EPCs, and subsequent administration of these EPCs to subjects at risk of restinosis.

Alitalo meets the limitations of the presently claimed invention because the claims read on methods of administration *before, during, or after* blood vessel damage, and Alitalo clearly contemplates administration of VEGF to subjects at risk of developing blood vessel damage (restinosis). The claims also read on administration of an ezrin-modulating agent, a cytokine, angiogenic factor, hematopoetic factor, or an effective fragment thereof, and VEGF is clearly a cytokine that is recognized as an angiogenic factor (column 3, lines 25-27). Furthermore, Alitalo teaches *ex vivo* administration of VEGF via a VEGF-encoding polynucleotide to EPCs followed by subsequent administration of these EPCs to a subject, and while Alitalo does not specifically teach ex vivo administration of VEGF polypeptide to EPCs, such use of VEGF polypeptides is clearly contemplated (see abstract and columns 3-5).

Although Alitalo does not specifically recite methods of modulating endothelial cell proliferation, inducing formation of new blood vessels, and methods of reducing the severity of tissue damage, it is noted that the administered agent of Alitalo (VEGF) is encompassed by the claimed invention as a preferred agent. Furthermore, the claims recite administration of ezrin-modulating agents *before, during, or after* blood vessel damage, and Alitalo clearly contemplates administration of VEGF before or during blood vessel damage so as to prevent restinosis. Therefore, because the therapeutic agent, patient populations, and method steps of Alitalo are the same as currently claimed, the VEGF of Alitalo would be expected, in absence of evidence to the contrary, to modulate endothelial cell proliferation, induce formation of new blood vessels, and/or reduce the severity of blood vessel damage in a subject.

***Conclusion***

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571)272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
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/Robert Landsman/
Primary Examiner, Art Unit 1647